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EXAMINER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,072	BROUGH, DOUGLAS E.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,39-42,45-48 and 50-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,39-42,45-48 and 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 30, 2009 has been entered.

The declaration by Douglas E. Brough on 06/26/2009 has been entered and considered.

Claims 1-34, 36-38, 43-44, and 49 are cancelled. Claims 35 and 46 have been amended. Claims 35, 39-42, 45-48, and 50-53 are pending and currently under examination.

This application 10/586,072 is a 371 of PCT/US04/04891 filed on 02/19/2004, which is a Continuation-in-part of US application 10/373,249 filed on 02/24/2003, abandoned on 01/18/2007.

Claim Objection

2. Previous objection of claim 35 is withdrawn because **(i)** the limitation "*Hath1*" recited in claim 35 has been amended to recite "Hath1" to refer the protein encoded by *Hath1*; and **(ii)** the limitation "a pharmaceutical composition comprising a subgroup A, B, D, E, or F adenoviral vector comprising a nucleic acid sequence ---" recited in claim 35 has been amended to recite "a pharmaceutical composition comprising an adenoviral vector selected from the group consisting of adenoviral vector A, B, D, E, and F subgroups, wherein the adenoviral vector comprises a nucleic acid sequence ---".

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

3. Previous rejection of claims 35, 39-42, 45-48, and 50-53 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended.

Claims 35 has been amended to recite "operably linked to a promoter that functions in supporting cells of inner ear" instead of previously recited "operably linked to a promoter that specifically functions in supporting cells of inner ear". This withdrawn rejection was based on that no disclosure from specification or status of art clearly states what promoter(s) is/are considered as "specifically functions in supporting cells of the inner ear", as recited previously in claim 35. Therefore, the metes and bounds of previously recited limitation "a promoter that specifically functions in supporting cells of the inner ear" was unclear. Claims 39-42, 45-48, and 50-53 depend from claim 35.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Previous new matter rejection of claims 35, 39-42, 45-48, and 50-53 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is ***withdrawn*** because Applicant's arguments in combination with claim amendments filed on 03/30/2009 have been fully considered and found persuasive.

(i) The aspect of the rejection pertaining to the limitation "a promoter that specifically functions in supporting cells of the inner ear" is *withdrawn* because claim 35 has been amended to recite "a promoter that functions in supporting cells of the inner ear".

(ii) The aspect of the rejection pertaining to the limitation "a pharmaceutical composition comprising a subgroup A, B, D, E, or F adenoviral vector comprising a nucleic acid sequence encoding Hath1 operably linked to a promoter ---" is *withdrawn* because claim 35 has been amended to recite "a pharmaceutical composition comprising an adenoviral vector selected from the group consisting of adenoviral vector A, B, D, E, and F subgroups, wherein the adenoviral vector comprise a nucleic acid sequence encoding Hath1 operably linked to a promoter ---".

Applicant argues that paragraph [0025] disclosed in the specification discloses the following statements: "However, non-group C adenoviruses, and even non-human adenoviruses, can be used to prepare replication-deficient adenoviral gene transfer vectors for delivery of DNA to target cells in the inner ear". Applicant argues that the statement disclosed paragraph [0025] in combination with adenoviral serotypes: subgroup A, subgroup B, subgroup C, subgroup D, subgroup E, and subgroup F, disclosed in paragraph [0025] in the specification support expression of *Hath1* gene from adenoviral vector A, B, D, E, and F subgroups recited in claim 35. Applicant's arguments in combination with claim amendments filed on 03/30/2009 have been fully considered and found persuasive.

Scope of Enablement

5. Previous scope of enablement rejection of claims 35, 39-42, 45-48, and 50-53 under 35 U.S.C. 112, first paragraph, is ***withdrawn*** because the claim 35 has been amended to delete "specifically" in the phrase "specifically function ---" and to recite "a nucleic acid sequence encoding Hath1 operably linked to a promoter functions in supporting cells of the inner ear". Claims 39-42, 45-48, and 50-53 depends from claim 35.

This withdrawn scope of enablement was documented as the specification, while being enabling for a method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising an adenoviral vector comprising a nucleic acid sequence encoding an atonal-associated factor Math1 (also known as Hath1 and Atoh1) operably linked to a promoter that drives gene expression in supporting cells of the ear, wherein the nucleic acid sequence is expressed to produce Math1 in supporting cells of the inner ear resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear, **does not** reasonably provide enablement for an adenoviral vector that expresses any atonal-associated factor other than Math1 driven by a tissue specific promoter that drives expression specifically in the supporting cells of the inner ear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 35, 39, 40, 50, and 51 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006). Applicant's arguments filed on 03/30/2009 have been fully considered and found not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 14-17 of the office action mailed on 12/28/2008.

Previous rejection is ***maintained*** for the reasons of record advanced on pages 14-17 of the office action mailed on 12/18/2008, is revised below in this office action to address claim amendments filed on 03/30/2009.

Claim 35 file don 03/30/2009 has been amended to read as follows: A method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising an adenoviral vector selected from the group consisting of adenoviral vector a subgroup A, B, D, E, and F subgroups, wherein the adenoviral vector comprises adenoviral vector comprising a nucleic acid sequence encoding Hathl operably linked to a promoter that functions in supporting cells of the inner ear, wherein the nucleic acid sequence is expressed to produce Hathl resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

Zoghbi et al. disclose a method of generating hair cells for an animal comprising delivering directly to an inner ear of said animal an human atonal associated nucleic acid

encoding the polypeptide Hath1 (SEQ ID No: 58, 354 amino acid, columns 127-129) (see lines 25-33, col. 5, and claim 3), and Hath1 is a transcription factor belonging to the basic helix-loop-helix (bHLH) family of proteins (See lines 30-32, col. 1). Zoghbi et al. also disclose such a method wherein the animal is a human, the atonal associated factor is Hath1, the vector is a viral vector, an adenoviral vector, an adeno-associated viral vector, replication deficient (E1) adenoviral vector, and the hair cells are generated from adult differentiated cells of inner ear (see col.139, claims 1-8, and col. 47, lines 37-56, col. 48, example 16). Zoghbi et al teaches that in a preferred embodiment said vector is an adenovirus vector comprising a cytomegalovirus (CMV) IE promoter sequence and a SV40 early polyadenylation signal sequence (See for instance lines 46-50, column 16, Zoghbi et al.). It is worth noting that, In Example 2 of instant application, the Math1 cDNA, which encodes a mouse atonal-associated factor, is operatively linked to the same cytomegalovirus immediate early (CMV) promoter as disclosed by Zoghbi et al.

Zoghbi et al. further disclose that different methods of delivery can be utilized to administer a vector into a cell. Examples include: (1) methods utilizing physical means, such as electroporation (electricity), a gene gun (physical force) or applying large volumes of a liquid (pressure); and (2) methods wherein said vector is complexed to another entity, such as a liposome, viral vector or transporter molecule (which binds to cell surface receptor, see col. 27, 2nd paragraph) (reading on claim 21 of instant application).

With regard to changing the sensory perception of an animal by expressing Hath1 recited in claim 35, Zoghbi et al. teach methods of treating an animal, including a human, for treating hearing impairment or an imbalance disorder by administration of a vector expressing the atonal associated factor Hath1 (See for instance, second paragraph, col. 5).

With regard to hes-1 promoter (claim 39 of instant application), Zoghbi et al. teaches that it is also possible, and often desirable, to use promoter or control sequences normally associated with the Math1 gene sequence, provided such control sequences are compatible with the host cell systems or the target cell (See Example 15). In this regard, Zoghbi et al. cites Zine et al., 2001, which taught that Hes1 and Hath1 are expressed in the developing cochlea of inner ears (Zine et al., Hes1 and Hes5 activities are required for the normal development of the hair cells in the mammalian inner ear, *The Journal of Neuroscience*, vol. 21, pp. 4712-4720, 2001).

However, Zoghbi et al. do not teach subgroup A, B, D, E, or F adenoviral vector.

Regarding subgroup A, B, D, E, or F adenoviral vector, **Falck-Pedersen et al.** specifically teaches the limitations on the use of group C adenoviral gene therapy vectors because a host can develop an immune response to the particular adenoviral vector being used in gene therapy as a result of natural exposure of the host to the same type of adenovirus prior to the initiation of gene therapy or as a result of the exposure of the host to the adenoviral vector in the course of the gene therapy itself (See lines 34-40 column 6, Falck-Pedersen et al.). Falck-Pedersen et al. characterized the oncogenic potential of adenoviral vectors of different subgroups (See Table, columns 1-2, Falck-Pedersen et al.), and examined the similarities and differences between various adenovirus groups by comparing the amino acid similarity and identity between the E1A and E1B gene products of Ad2 (group C), Ad5 (group C), Ad7 (group B), Ad12 (group A), and Ad40 (group F) adenoviruses (See Example 5, Falck-Pedersen et al.)

It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor to the inner ear of a subject as taught by Zoghbi et al. using the adenoviral vector belonging to subgroup A,

B, D, E, or F to circumvent host immunity taught by the teachings of Falck-Pedersen et al. because the presence of immune response to subgroup C adenovirus prevent efficacious adenovirus vector administration *in vivo*.

As such, the ordinary artisan would have been motivated to use the adenoviral vector belonging to subgroup A, B, D, E, or F to deliver nucleic acid sequence encoding Hath1 *in vivo* because its effectiveness in expressing the gene of interest *in vivo* without provoking undesired host immunity to the adenoviral vector.

The level of skill in art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to replace the native coat protein with an engineered coat protein in an adenoviral vector of subgroup A, B, D, E, or F, and deliver it to inner ear to generate sensory hair cells.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments and response to applicant's arguments

Applicant's argues that there is no suggestion to combine the cited references and that it is unexpected results of subgroup B (Ad35) and subgroup D (Ad28) adenoviral vectors enhancing delivery of gene of interest to sensoru cells of the inner ear as compared to the delivery by a subgroup C adenoviral vector (i.e. Ad5) as staed in the Declaration under 37 C.F.R. § 1.132 of Douglas E. Brough filed on 02/26/2009 (pages 9-10 of Applicant's remarks filed on 03/30/2009).

In response, the Examiner notes that, as stated in the maintained rejection on the advisory action mailed on 03/23/2009, it would have been obvious to one of ordinary skill in the art to

combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor to the inner ear of a subject as taught by Zoghbi et al. using the adenoviral vector belonging to subgroup A, B, D, E, or F to circumvent host immunity taught by the teachings of Falck-Pedersen et al. because the presence of immune response to subgroup C adenovirus preventing efficacious adenovirus vector administration *in vivo*. As such, the ordinary artisan would have been motivated to use the adenoviral vector belonging to subgroup A, B, D, E, or F to deliver nucleic acid sequence encoding Hath1 *in vivo* because its effectiveness in expressing the gene of interest *in vivo* without provoking undesired host immunity to the adenoviral vector. The level of skill in art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to replace the native coat protein with an engineered coat protein in an adenoviral vector of subgroup A, B, D, E, or F, and deliver it to inner ear to generate sensory hair cells. Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

With regard to the asserted requirement for teaching, suggestion, or motivation to render obviousness, the Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc. that forecloses the argument that a specific teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

The arguments of unexpected results of subgroup B (Ad35) and subgroup D (Ad28) adenoviral vectors enhancing delivery of gene of interest to sensoru cells of the inner ear as compared to the delivery by a subgroup C adenoviral vector (i.e. Ad5) as staed in the Declaration under 37 C.F.R. § 1.132 of Douglas E. Brough filed on 02/26/2009, have been fully considered and found not persuasive. It is unclear to the examiner how the expression of reporter gene GFP driven by CMV promoter in the transfected *in vitro* utricle cell culture is enhanced by subgroup B (Ad35) and subgroup D (Ad28) adenoviral vectors as compared to a subgroup C adenoviral vector (i.e. Ad5) stated in the declaration can be used to support the limitation "A method of changing the sensory perception of an animal" and "resulting ingeneration of sensory hair that allow perceptionof stimuli in the inner" recited in claim 35. Furthermore, it is unclear why the declared "enhanced" GFP expression by Ad35 or Ad 28 is unexpected because a subgroup C adenoviral vector (i.e. Ad5) is the first generation of adenoviral vector and subgroup B (Ad35) and subgroup D (Ad28) adenoviral vectors were developed later to overcome the issues researchers had experienced with Ad5 mediated gene expression for genes therapy purposes.

7. Claims 41 and 42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005), in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006) as applied to claims 35, 39, 40, 50, and 51above, and further in view of **Kovesdi et al.** (US patent 6,821,775, issue date, Nov. 23, 2004). Applicant's arguments filed on 03/30/2009 have been fully considered and found not persuasive. Previous rejection is

maintained for the reasons of record advanced on pages 17-19 of the office action mailed on 12/28/2008.

The teachings of Zoghbi et al. and Falck-Pedersen et al. are set forth in the rejection of claims 35, 39, 40, 50, and 51 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005) in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998).

However, neither Zoghbi et al. nor Falck-Pedersen et al. teaches such a method wherein an adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region.

Regarding an adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region, Kovesdi et al. teach a replication deficient adenoviral vector with deletion of E1 and E4 and further comprise a pGUS spacer in the E4 region (see second paragraph, col. 7 and claim 1). Kovesdi et al. also disclose that said vector is used to deliver therapeutic effective amount of PEDF to eyes of mice to promote neovascularization. Kovesdi et al. further discloses that in the absence of a spacer, production of fiber protein and/or viral growth of the multiply replication deficient adenoviral vector is reduced by comparison to that of a singly replication deficient adenoviral vector. However, inclusion of the spacer in at least one of the deficient adenoviral regions, preferably the E4 region, counteracts this defect in growth and fiber expression (See third paragraph, col. 6, and claim 1).

It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding Hath1 to the inner ear of a subject as taught by Zoghbi et al. using the adenoviral vector of subgroup A, B, D, E, or F that circumvents host immunity taught by combined teachings of Falck-Pedersen et al. because the presence of

immune response to the subgroup C adenoviral vector prevent efficacious adenovirus vector administration *in vivo*. Furthermore, It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by combined teachings of Falck-Pedersen et al., and Kovesdi et al. in the method of generating hair cells to deliver atonal associated nucleic acid to inner ear of a subject taught by Zoghbi et al. because the vector taught by combined teachings of Falck-Pedersen et al. and Kovesdi et al. is able to (i) counteract the defect in growth of the E1/E4 deficient ADV and the defect in expression of the coat protein, and (ii) circumvent host immunity against adenoviral vector subgroup C.

As such, the ordinary artisan would have been motivated to use this vector to deliver atonal associated nucleic acid *in vivo* because of (i) its effectiveness in expressing a gene of interest *in vivo* without provoking host immunity to the adenoviral vector belonging to subgroup A, B, D, E, or F, and (ii) capability of expressing the engineered coat protein in the adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region since Kovesdi et al. discloses that in the absence of a spacer, production of fiber protein and/or viral growth of the multiply replication deficient adenoviral vector is reduced by comparison to that of a singly replication deficient adenoviral vector; however, inclusion of the spacer in at least one of the deficient adenoviral regions, preferably the E4 region, counteracts this defect in growth and fiber expression (See third paragraph, col. 6, and claim 1).

One of ordinary skill in the art would have reasonable expectation of success in delivering a nucleic acid sequence such encoding Hath1, to inner ear to generate sensory hair cells because the adenoviral vector of subgroup A, B, D, E, or F taught by combined teachings of Falck-Pedersen et al and Kovesdi et al can be used for proper expression of a exogenous gene

such Hath1 due to the presence of deficiency in both E1 and E4 and the presence of a spacer in E4 region.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments and Examiner's ***Resposne to Applicant's arguments*** are the same as documented in the rejection of claims 35, 39, 40, 50, and 51 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. in view of Falck-Pedersen et al.

8. Claims 45-48 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006) as applied to claims 35, 39, 40, 50, and 51above, and further in view of **Staecker et al.** (Staecker et al., Brain-derived neurotrophic factor gene therapy prevents spiral ganglion degeneration after hair cell loss. *Otolaryngol Head Neck Surg.* 119(1): 7-13, 1998; listed as reference EU on the IDS filed by Applicant on 11/16/2006). Applicant's arguments filed on 03/30/2009 have been fully considered and found not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 19-21 of the office action mailed on 12/28/2008.

The teachings of Zoghbi et al. and Falck-Pedersen et al. are set forth in the rejection of claims 35, 39, 40, 50, and 51under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998).

However, neither Zoghbi et al. nor Falck-Pedersen et al. teaches such a method wherein a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor is also administered with the atonal associated factor Hath1.

Regarding a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor is also administered with the atonal associated factor, Staecker et al. teach brain-derived neurotrophic factor (BDNF) gene therapy prevents spiral ganglion degeneration after hair cell loss by supporting the survival of auditory neurons (see abstract, bridging paragraph between left and right columns, page 10, and Figure 5).

It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor Hath1 to the inner ear of a subject as taught by Zoghbi et al. using the adenoviral vector of subgroup A, B, D, E or F that circumvents host immunity taught by Falck-Pedersen et al. because the presence of immune response to the subgroup C adenoviral vector prevents efficacious adenovirus vector administration *in vivo*. It would have been obvious to one of ordinary skill in the art to co-administer neurotrophic agent such as BDNF with atonal associated factor Hath1 in the method of changing sensory perception based on the combined teaching of Zoghbi et al., Falck-Pedersen et al., and Staecker et al.

One of ordinary skill in the art would have been motivated to include BDNF in the claimed method because BDNF has been shown by Staecker et al. to support the survival of auditory neurons. If the ordinary artisan intends to generate hair cells and improve hearing after

hearing loss, the ordinary artisan would be motivated to preserve the auditory neurons which are vital for hearing.

The level of skill in the art is high. One of ordinary skill in the art would have reasonable expectation of success to co-administer the BDNF with atonal associated factor using a separate or the same vector in the method taught by Zoghbi et al. and Falck-Pedersen et al. because of the demonstration that a subgroup A, B, D, E, or F adenoviral vector can circumvent host immunity against subgroup C adenoviral vector by the combined teachings of Falck-Pedersen et al., and the demonstration that brain-derived neurotrophic factor (BDNF) gene therapy prevents spiral ganglion degeneration after hair cell loss by supporting the survival of auditory neurons by the teachings of Staecker et al.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments and Examiner's ***Resposne to Applicant's arguments*** are the same as documented in the rejection of claims 35, 39, 40, 50, and 51 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. in view of Falck-Pedersen et al.

9. Claims 52 and 53 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006) as applied to claims 35, 39, 40, 50, and 51above, and further in view of **Wickham et al.** (Wickham et al., US 6,455,314, issued 09/24/2002; This patent is listed as reference BM on the IDS filed by Applicant on 11/16/2006) and **Mizuguchi et al.** (Mizuguchi et

al., CAR- or αv integrin-binding ablated adenovirus vectors, but not fiber-modified vectors containing RGD peptide, do not change the systemic gene transfer properties in mice, *Gene Ther.* 9(12):769-76, 2002). Applicant's arguments filed on 03/30/2009 have been fully considered and found not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 23-24 of the office action mailed on 12/28/2008.

The teachings of Zoghbi et al. and Falck-Pedersen et al. are set forth in the rejection of claims 35, 39, 40, 50, and 51under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998).

However, neither Zoghbi et al. nor Falck-Pedersen et al. teaches an adenoviral vector mediated gene therapy with an alternatively targeted adenovirus.

Regarding an adenoviral vector with altered target cells (claims 52 and 53 of instant application), Wickham et al, teaches that coxsackievirus and adenovirus receptor (CAR) is the receptor for adenovirus serotype 2 and 5, citing (Bergelson et al., Science, 275, 1320-23 (1997) (See lines 35-40, col. 1), and mutations reducing affinity of adenovirus for the CAR protein (See Table 2 and Table 3). Mizuguchi et al. teaches that targeted gene delivery to the tissue of interest by recombinant adenovirus (Ad) vectors is limited by the relatively broad expression of the primary receptor, the coxsackievirus and adenovirus receptor (CAR), and the secondary receptor, αv integrin; and this problem could be overcome by mutating the fiber and penton base, which bind with CAR and αv integrin, respectively.

It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by the combined teachings of Zoghbi et al. and Falck-Pedersen et al. in the method of

generating hair cells to deliver nucleic acid encoding Hath1 to inner ear of a subject since the vector taught by combined teachings of Zoghbi et al. and Falck-Pedersen et al. that circumvents host immunity against adenoviral vector of subgroup C. It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by combined teachings of Falck-Pedersen et al., Wickham et al., and Mizuguchi et al. in the method of generating hair cells to deliver nucleic acid encoding Hath1 to inner ear of a subject taught by Zoghbi et al. because the vector taught by combined teachings of Falck-Pedersen et al., Wickham et al., and Mizuguchi et al. not only circumvents host immunity, but also successfully targets adenovirus to different cell types expressing different receptors of an adenoviral vector *in vivo*.

As such, the ordinary artisan would have been motivated to use the vector taught by combined teachings of Falck-Pedersen et al., Wickham et al., and Mizuguchi et al. to deliver nucleic acid encoding Hath1 *in vivo* because its effectiveness in expressing the gene of interest *in vivo* in desired target cell types, without provoking host immunity to the adenoviral vector of subgroup A, B, D, E, or F.

The level of skill in art of molecular cloning is high. One of ordinary skill in the art would have reasonable expectation of success to replace the native coat protein with altered coat protein, and deliver the adenoviral vector to desired target cells in inner ear to generate sensory hair cells because the adenoviral vector comprises engineered coat protein taught by combined teachings of Falck-Pedersen et al., Wickham et al., and Mizuguchi et al. can be used to express therapeutic gene *Hath1* into cells of inner ear taught by Kovesdi et al., and the altered ligand-receptor interaction taught by Wickham et al. and Mizuguchi et al. can result in the adenoviral virus targeting to desired cells expressing different receptors of an adenoviral vector *in vivo* .

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments and Examiner's ***Resposne to Applicant's arguments*** are the same as documented in the rejection of claims 35, 39, 40, 50, and 51 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. in view of Falck-Pedersen et al.

Conclusion

10. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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